Remarks and Arguments

Claims 1-18 were pending prior to this amendment. Claims 1, 12 and 14 have been amended to correct typographical errors reciting "a typical" or "typical" depression rather than "atypical" depression. Claim 4 has been amended to delete "derivatives" and correct the spelling of "stereoisomer." Claim 11 reads on triple reuptake inhibitors (TRIs) and was inadvertently included among the claims that read on milnacipran in the Response to Restriction Requirement. Accordingly, claim 11 has been withdrawn. Claim 13 has been amended to correct a typographical error reciting "a typical" chest pain rather than "atypical" chest pain. Claims 15-18, directed to milnacipran pharmaceutical compositions, have been canceled.

The objections

The Examiner contends that (1) the Information Disclosure Statements filed November 21, 2003 and March 1, 2004 do not comply with the patent rules because they do not include a concise explanation of the relevance of each document, and (2) the claims contain non-elected subject matter.

37 C.F.R. § 1.98(a) requires a concise explanation of the relevance of each patent, publication, or other information listed in an Information Disclosure Statement that is not in the English language. One of the disclosed references, Strolin-Benedetti, Encephale 1982;8(5):545-585 ("Strolin"), is not in the English language. A concise explanation of the relevance of Strolin is provided in its "Summary" (Strolin, page 545) (copy attached as Exhibit 1). Accordingly, this objection should be withdrawn.

Applicant respectfully submits that there is no requirement that elected claims be amended to delete non-elected subject matter. In fact, the patent rules permit claims directed to a reasonable number of species. See 37 CFR §1.146. Thus, this objection should be withdrawn.

According to the Examiner, two references (Joyce 2002 and Paykel 1983) "were not present in the file and could not be considered." Applicant respectfully notes that these references were scanned into the Patent & Trademark Office's PAIR database with the Information Disclosure Statement filed November 19, 2003. Accordingly, Applicant requests that these references be considered.

The rejections for lack of enablement under 35 U.S.C. § 112, first paragraph and indefiniteness under 35 U.S.C. § 112, second paragraph

The Examiner contends that the specification does not enable the full scope of claims 4-6 because it is not clear what compounds would be included in the term "derivatives," and "it would take undue experimentation to determine which compounds would yield the active compound." (Office Action, page 3). Further, the Examiner has rejected claims 4-6 as indefinite because it "is confusing as to whether all of each sterioisomeric forms, mixtures of sterioisomeric forms, metabolites, derivatives, or pharmaceutically acceptable salts are required."

Claim 4 has been amended to delete "derivatives" and recite "a stereoisomeric form, mixtures of stereoisomeric forms, metabolite or pharmaceutically acceptable salt." Thus, the rejections under 35 U.S.C. § 112, first and second paragraphs should be withdrawn.

The claim rejection for anticipation

The Examiner alleges that claims 15-17 are anticipated by U.S. Patent No. 4,478,836 (Mouzin). According to the examiner, Mouzin discloses milnacipran and formulations of milnacipran that deliver a dosage greater than the dosage required to treat typical depression. The Examiner acknowledges that Mouzin does not disclose the use of milnacipran to treat atypical depression. However, the Examiner contends that intended use does not impart patentability to a composition claim.

This rejection is obviated by the cancellation of claims 15-17.

The rejection of claim 18 under 35 U.S.C. § 103(a)

Claim 18 has been rejected as obvious over Mouzin in view of U.S. Patent No. 5,942,549. This claim is directed to a pharmaceutical composition comprising at least two of milnacipran, sibutramine, and an aminocyclopropane derivative.

According to the Examiner, Mouzin discloses milnacipran, its dosage, and its use to treat depression; and '549 discloses the use of sibutramine for the treatment of depression. The Examiner contends that it would have been obvious to combine milnacipran and sibutramine because each agent was known to be useful for the treatment of depression.

This rejection is obviated by the cancellation of claim 18.

The first rejection of claims 1-17 under 35 U.S.C. § 103(a)

Claims 1-17 have been rejected as obvious over Mouzin in view of Dworkin et al., Clin J Pain 1991;7(2):79-94 (abstract) or Ruoff et al., J Fam Practice 1996;43(Suppl 6):S25-S34 (abstract) and Quitkin et al., Arch Gen Psychiatry 1989;46:787-93. According to the Examiner, Quitkin discloses that atypical depression is a subgroup of depression that is indistinguishable from simple mood depression except for the presence of at least one vegetative atypical sign, and that "both forms of depression respond to many of the same compounds" (Office Action, page 5). The Examiner contends that Dworkin and Ruoff disclose that chronic pain patients often have depressive disorders. Thus, the Examiner concludes that it would have been obvious to use milnacipran to treat DSP because it responds to many of the same compounds used to treat simple mood depression.

Applicant respectfully traverses this rejection. Quitkin discloses that a monoamine oxidase inhibitor (phenelzine) was effective for the treatment of both simple depression and atypical depression. A tricyclic antidepressant (imipramine) was effective for the treatment of simple depression, but not atypical depression (Quitkin, page 792, 2nd paragraph under "Comment").

Ruoff discloses that "[t]he relationship between chronic pain and depression is complex and not entirely understood" (Ruoff, 3rd paragraph).[1]

Dworkin discloses that the response to the treatment of chronic pain differs between patients with and without depression. The assessment of depression in Dworkin was made by pain specialists and not by psychiatrists or psychologists (Dworkin at 346). Further, the diagnoses were not based on standardized criteria. *Id.* Dworkin concludes that:

> "It would be valuable to extend our study .... One worthwhile method would be to use recent standardized diagnostic criteria for depression.... There are clearly several different types of affective disorder that are found in chronic pain patients [lists four, including atypical depression] that would seem to be especially relevant to chronic pain. Because important differences may well exist within the group of depressed pain patients, a richer and ultimately more valid approach to the questions we have examined would address such heterogeneity." *Id.* at 351.

[1] Copies of the entire Ruoff and Dworkin references are provided with the accompanying Information Disclosure Statement.

The combination of references cited by the Examiner teach that: (1) different types of depression are associated with chronic pain, (2) the relationship between chronic pain and depression is complex and not well understood, and (3) treatments for simple depression may not work for atypical depression. Thus, the treatment of atypical depression is unpredictable, no reference provides the motivation to use milnacipran for the treatment of atypical depression, and none of the references provides a reasonable expectation that treating atypical depression with milnacipran would be successful. Accordingly, this rejection should be withdrawn.

The second rejection of claims 1-17 under 35 U.S.C. § 103(a)

Claims 1-17 have been rejected as obvious over Davidson et al., Arch Gen Psychiatry 1982;39:527-34 in view of Palmier et al., Eur J Clin Pharmacol 1989;37(3):235-38 and Dworkin or Ruoff. The Examiner alleges that Davidson discloses the use of MAO inhibitors to treat DSP, and Palmier discloses that milnacipran is a MAO inhibitor. The Examiner does not state why one of ordinary skill in the art would have been motivated to combine these references.

Applicant respectfully traverses this rejection. Davidson discloses the superiority of monoamine oxidase (MAO) inhibitors over placebo for the treatment of atypical depression. Palmier discloses that milnacipran inhibits the "uptake of both monoamines," i.e., noradrenaline and 5-HT (Palmier at 237).

Contrary to the Examiner, milnacipran is not a MAO inhibitor. Milnacipran inhibits the reuptake of the monoamines norepinephrine and serotonin, but does not inhibit the enzyme monoamine oxidase. Dual reuptake inhibitors such as milnacipran and MAO inhibitors are different. For example, the co-administration of mixed norepinephrine/serotonin reuptake inhibitors and MAO inhibitors is contraindicated (see, e.g., Harrison's Principles of Internal Medicine, 15th edition, Table 385-3, page 2544) (copy attached as Exhibit 2). Accordingly, no combination of these references discloses or suggests treating atypical depression with milnacipran.

Conclusion

No new matter has been added by these amendments. In view of the comments and amendments set forth above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: February 28, 2006

Respectfully submitted,

By _____

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